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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,350	07/11/2003	John K. Cini	MXI-285	6687

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EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	
MAIL DATE	**DELIVERY MODE**
12/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,350	CINI ET AL.	
	Examiner	Art Unit	
	RUIXIANG LI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,9-13,15,17-21,23,25,26,29-31,33 and 35-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 9-13, 15, 17-21, 23, 25, 26, 29-31, 33, 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/2008 are entered. Claims 4, 5, and 27 are canceled. Claims 1, 3, 9-13, 15, 17-21, 23, 25, 26, 29-31, 33, and 35-39 are pending and under consideration.

Withdrawn Objections and/or Rejections

The rejection of claims 1, 3-5, 9-13, 15, 17-21, 23, 25-27, 29-31, 33, and 35-39 under 35 U.S.C.112, first paragraph is withdrawn in view of amended and canceled claims.

Claim Rejections under 35 USC § 103 (a)

(i). The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(ii). Claims 1, 3, 9-13, 15, 17-21, 23, 25, 26, 29-31, 33, and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kerwin et al. (US Patent No. 5,929,031, 27 July 1999), and further in view of Hagiwara et al. (U.S. Patent No. 6,165,467, December 26, 2000), Packer et al. (*Methods in Enzymology,* Volume 186:41-42, 1990), and Akers (*J. Par. Sci. Tech.* 36:222-228, 1982).

Kerwin et al. teach preparation of a pharmaceutical composition (column 8), which comprises a protein, hemoglobin at a concentration of 0.001% to 90% (w/v) (4 mg/ml and 100 mg/ml were used in Example 1 and 2), a reducing agent, such as sodium ascorbate or 0.03% (w/v) polysorbate 80 (lines 24-25 of column 13), chelators, such as 0-200 μM of DTPA and/ or EGTA (lines 45-51 of column 8). The formulation may also comprise one or more buffers, such as citrate or Tris (line 65 of column 12), and salts, such as sodium chloride (lines 32-35). The pH of the composition can be at about 6.5-9.5 (line 52 of column 8).

Kerwin et al. do not teach preparing a formulation comprising an antibody, a monoclonal antibody or a human antibody formulated with DTPA and DEF or a method of preparing such a composition.

Hagiwara et al. teach preparing a stable human monoclonal antibody preparation (see, e.g., Abstract). Hagiwara et al. also teach human monoclonal antibodies have an undesirable property that they easily aggregate and precipitate in a

solution state (the 4th paragraph of column 1).

Packer et al teach a chelating agent, desferrioxamine (deferoxamine or DEF), which suppresses ion-dependent generation of ·OH from H_2O_2 (the 2nd paragraph of page 42).

Therefore, it would have been obvious to one of skilled in the art to modify the method of Kerwin et al. to prepare a composition comprising a human monoclonal antibody formulated with DTPA and DEF with a reasonable expectation of success. One would have been motivated to do so because Kerwin et al. teach that one or more chelators can be used in a formulation (lines 45-51 of column 8) and Akers teaches that the use of combination of antioxidant in the same formulation produces a synergistic effect (page 227, the 2nd paragraph). Moreover, a human monoclonal antibody is, in essence, a protein and shares the basic components—amino acids with a protein, including cysteine residues, which are susceptible to oxidation. A human monoclonal antibody possesses characteristics that tend to form aggregates as taught by Hagiwara et al. (the 4th paragraph of column 1). The use of DTPA and DEF would stabilize a composition comprising a human monoclonal antibody.

Response to Applicants' argument

Applicants argue that Applicants have amended independent claims 1 and 23 to specify particular concentrations ranges for both DTPA and DEF. Applicants

argue that none of the cited references, either alone or in combination, teach or suggest the presently claimed composition, let alone the particular concentration ranges, as presently claimed.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth immediately above. Moreover, since the concentration range of a chelating agent taught by Kerwin et al. is 0-200 μM, which overlaps with the concentration ranges of DTPA and DEF recited in claims 1 and 27, a prima facie case of obviousness exists (See MPEP 2144.05, Obviousness of Ranges).

(iii). Claims 1, 3, 9, 10, 12, 13, 15, 17-21, 23, 25, 26, 29-31, 33, and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 5,217,954 A, 8 June 1993) in view of Hagiwara et al. (U.S. Patent No. 6,165,467, December 26, 2000), Packer et al. (*Methods in Enzymology*, Volume 186: 41-42, 1990), and Akers (*J. Par. Sci. Tech.* 36:222-228, 1982).

Foster et al. teach protection of bFGF from oxidation during storage and clinical use. Foster et al. teach the presence of certain chelating agents effectively stabilizes this protein against oxidation of its free cysteine residues or metal-induced aggregation (bottom of column 1).

Specifically, Foster et al. teach preparation of a pharmaceutical formulation comprising a protein, bFGF, a stabilizing chelator, such as DTPA or EGTA. The formulation comprises optionally an agent for tonicity, a preservative or other auxiliaries, such as mannitol, glycerol, sodium chloride (see, e.g., columns 3-6) or Tris (Example 1). The concentration of chelating agent is present in amounts of from about 0.001% to about 2.0% percent (weight/weight) of the overall formulation (the 4th paragraph of column 4), which is about 0.025 mM to 50 mM for DTPA (molecular weight of DTPA is 393), and 0.018 to 36 mM for DEF (molecular weight of DEF is 561). Foster et al. teach that the chelators are used individually or in combinations (bottom of column 1 to top of column 2) and that a stabilizer can be used in combination with other stabilizers, such as citrate (the 2nd paragraph of column 5) and that the formulation can be prepared in a buffer system, such as sodium citrate (the 4th paragraph of column 5), with the pH of the formulation being from about 2 to about 8 (the 6th paragraph of column 5).

Foster et al. teach continuous release formulations, including microcapsules that are essentially small particles of active compounds embedded in a suitable polymer (the 4th paragraph of column 5). Foster et al. further teach that the formulation comprises 0.01%-10% FGF in solution (lines 48-49 of column 6, and in Example 4, the concentration of FGF is 100 ug/ml).

Foster et al. do not teach a composition comprising an antibody formulated with

DTPA and DEF or a method preparing such a composition.

Hagiwara et al. teach preparing a stable human monoclonal antibody preparation (see, e.g., Abstract). Hagiwara et al. also teach human monoclonal antibodies have an undesirable property that they easily aggregate and precipitate in a solution state (the 4th paragraph of column 1).

Packer et al. teach a chelating agent, desferrioxamine (deferoxamine or DEF), which suppresses iron-dependent generation of ·OH from H_2O_2 (2nd paragraph of page 42).

Therefore, it would have been obvious to one of skilled in the art to modify the method of Foster et al. to prepare a composition comprising a human monoclonal antibody, formulated with DTPA and DEF with a reasonable expectation of success. One would have been motivated to do so because Foster et al. teach that the chelators can be used either individually or in combination (bottom of column 1 to top of column 2) and Akers teaches that the use of combination of antioxidant in the same formulation produces a synergistic effect (page 227, the 2nd paragraph). Moreover, a human monoclonal antibody is, in essence, a protein and shares the basic components—amino acids with a protein, including cysteine residues, which are susceptible to oxidation. A human monoclonal antibody possesses characteristics that tend to form aggregates as taught by Hagiwara et al. (the 4th paragraph of column 1). The use of DTPA and DEF would stabilize a

composition comprising a human monoclonal antibody.

Response to Applicants' argument

Applicants argue that Applicants have amended independent claims 1 and 23 to specify particular concentrations ranges for both DTPA and DEF. Applicants argue that none of the cited references, either alone or in combination, teach or suggest the presently claimed composition, let alone the particular concentration ranges, as presently claimed.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth immediately above. Moreover, since the concentration range of a chelating agent taught by Foster et al. is equivalent to about 0.025 mM to 50 mM for DTPA, and 0.018 to 36 mM for DEF, which overlap with the concentration ranges of DTPA and DEF recited in claims 1 and 27, a prima facie case of obviousness exists (See MPEP 2144.05, Obviousness of Ranges).

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday

from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

/Ruixiang Li/
Primary Examiner, Art Unit 1646

Ruixiang Li, Ph.D.
December 2, 2008